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10/572,348	12/18/2006	Jesper Lau	6692.204-US	7549

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NOVO NORDISK, INC.
INTELLECTUAL PROPERTY DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
11/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
KSHL@novonordisk.com
KISW@novonordisk.com

Office Action Summary	Application No.	Applicant(s)	
	10/572,348	LAU ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-146* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-77,83-89,95,100-105,107,109,111,114-116,118,119,123,126,128,138,140 and 141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 78-82,90-94,96-99,106,108,110,112,113,117,120-122,124,125,127,129-137,139 and 142-146.

DETAILED ACTION

Response to Election/Restriction filed on February 17, 2009 is acknowledged. Claims 75-146 are pending in this application.

Restriction

1. Applicant's election with traverse of Group 1 (claims 75-123, 126-128, 138 and 140-141), wherein the therapeutic polypeptide is GLP-1, and elected species of Example 61, wherein A is the penultimate formula on p. 14 of the application, W is –C(O)NH-, Y is –C(O)-, B is a hydrophilic spacer of claim 77 in which D=E=-O-, l=n=2, m=p=q=1 and in Q: Z is –C(O)NH-, D=G=-O-, l=n=m=3, an d p=0 in the reply filed on February 17, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL. Applicant indicates that claims 75-77, 83-92, 94-95, 100-105, 107, 109, 111-117, 118, 119, 121, 123, 128, 138 and 140-141 read on the elected species. However, the elected GLP-1 of example 61 is a GLP1 (7-37)-OH compound. Therefore, claims 112-113, 117 and 121 are further withdrawn from consideration, as being drawn to nonelected species. Therefore, claims 78-82, 93, 96-99, 106, 108, 110, 112, 113, 117, 120-122, 124-127, 129-137, 139, 142-146 are withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions and species, there being no allowable generic or linking claim. A search was conducted on the elected species and

this appears to be free of prior art. A search was extended to the other species, and these too also appear to be free of prior art. A search was extended to the broad Markush, and prior art was found. Claim 126 reads on the broad Markush claims and claims 90-92, 94 do not read on the elected species of the prior art. Therefore, claims 78-82, 90-94, 96-99, 106, 108, 110, 112, 113, 117, 120-122, 124-125, 127, 129-137, 139, 142-146 are withdrawn from further consideration. **Claims 75-77, 83-89, 95, 100-105, 107, 109, 111, 114-116, 118-119, 123, 126, 128, 138 and 140-141 are examined on the merits in this office action.**

Objection-Minor Informalities

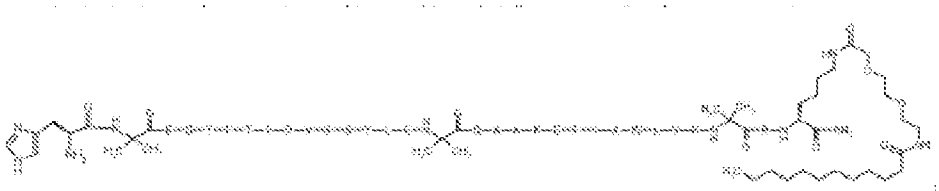
2. Claim 76 is objected to for the following minor informality: There appears to be a spelling error. Claim 76 recites at the last line of the claim, “sor a pharmaceutically acceptable salt of prodrug thereof.” The “sor” should be corrected to “or”.

3. Claim 76 is objected to for the following minor informality: The comma at line 7, before “wherein” should be moved up or associated with the formula “-P(OR^6)(O)-".

4. Claim 76 is objected to for the following reason: There appears to be a punctuation missing from the claim at the last line. The claim recites, “…wherein s is 0 or 1 sor a pharmaceutically acceptable salt or prodrug thereof.” There appears to be a punctuation missing between "1" and "sor".

5. Claim 77 is objected to for the following minor informality: The comma at the last line of the claim on page 2, prior to "wherein" should be moved up or associated with the formula “-P(OR^6)(O)-".

6. Claim 128 is objected to for the following reasons: Claim 128 recites amino acid sequences that comprise 4 or more amino acids. The peptide sequences are missing the sequence identifier. The proper way to claim a peptide sequence is for example,



(SEQ ID NO:1)

(see 37 CFR 1.821(d)). Furthermore, the claim appears to be missing punctuation at the end of the claim. The claim does not end with a period. These errors should be corrected.

Rejection-35 U.S.C. 112, 2nd

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 75-77, 88, 100-104, 107, 109, 111, 114-116, 118-119, 123, 138, 140-141 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 75 recite, “an albumin binding residue”. It is unclear what an albumin binding residue is. The instant specification discloses that “albumin binding residue means a residue which binds non-covalently to human serum albumin....A range of albumin binding residues are known among linear and branched lipophilic moieties containing 4-40 carbon atoms, compounds with a cyclopentanophenanthrene skeleton,

peptides having 10-30 amino acid residues, etc (see paragraph [0035] of instant specification US 2007/0203058 A1). According to the www.dictionary.com, a residue is something that remains after a part is removed; an atom or group of atoms considered as a group or part of a molecule (see definition enclosed). This definition and the specification implies that a residue is a part of a structure that binds an albumin compound. Therefore, it is unclear what components are encompassed within an albumin binding residue. Because claims 76-77, 88, 100-104, 107, 109, 111, 114-116, 118-119, 123, 138, 140-141 depend from indefinite claim 75 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

10. Claim 88 recites, "wherein the $-CH_2O[(CH_2)_2O)_m(CH_2)_pQ_q-$, where m is 1-10, p is 1-3, and Q is $Z-CH_2O[(CH_2)_2O]_m(CH_2)_p-$". It is unclear what the variable "q" is and if "m" and "p" is the same for the second formula as the first formula.

Rejection-35 U.S.C. 112, 1st

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 75-77, 83-89, 95, 100-105, 109, 111, 114-116, 118-119, 123, 126, 138, 140-141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing

date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of

certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

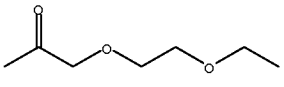
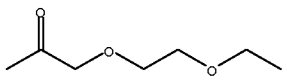
The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a compound which comprises a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer. Claims are further drawn to a compound wherein said GLP-1 peptide is selected from GLP-1(7-35), GLP-1(7-36)...or an analogue thereof. The generic statements a therapeutic polypeptide, an albumin binding residue, hydrophilic spacer, A is an albumin binding residue, B is hydrophilic spacer do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

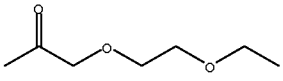
As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 75-77 are broad generics with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide or amide bonds, any class of bonds or linkers that can form bonds between two molecules or link two or more molecules together that are hydrophilic, and any peptide or peptide-like molecule that has a molar weight of less than 100 kDa, and any residue that functions to bind an albumin. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules that can from peptide or amide bonds, any amino acid mimetics that can form peptide or amide bonds and can be substituted

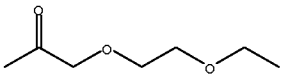
for a naturally occurring amino acid, and other synthetic peptide or peptide-like molecule that can bind to human GLP-1 receptor.

The specification discloses that “the term therapeutic polypeptide means a polypeptide which is being developed for therapeutic use, or which has been developed for therapeutic use" (see paragraph [0037] of instant specification US 2007/0203058 A1). Further, the specification discloses that "polypeptide and peptide means a compound composed of at least five constituent amino acids connected by peptide bonds" (see paragraph [0038] of instant specification as described above). The specification discloses that “the term analogue referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and/or wherein one or more amino acid residues have been deleted from thee peptide and or wherein one or more amino acid residues have been added to the peptide” (see paragraph [0039] of instant specification, as described above). The specification further discloses that “in one embodiment of the present invention the therapeutic polypeptide is a GLP-1 peptide” “GLP-1 peptide comprising the amino acid sequence of the formula (IV) (SEQ ID NO: 2), formula (V) (SEQ ID NO: 3), exendin-4 (SEQ ID NO: 4), ZP-10, SEQ ID NO: 5, GLP-2, human insulin or an analogue thereof, human insulin, human growth hormone or an analogue thereof, parathyroid hormone or an analogue thereof, human follicle stimulating hormone or an analogue thereof, and a list of polypeptide such as trypsin, papain (see paragraphs [0119]-[0219]). Claim 115 recites, "a compound wherein said GLP-1 peptide

comprises no more than ten amino acid residues which have been exchanged, added or deleted as compared to GLP-1 (7-37) (SEQ ID NO: 1); claim 116 recites “a compound wherein said GLP-1 peptide comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1 (7-37) (SEQ ID NO: 1). The specification is limited to  and $(CH_2)_4NH$-C(O)-$(CH_2)_3COOH$ as the linker. The specification discloses that an albumin binding residue is "a residue which binds non-covalently to human serum albumin. The albumin biding residue attached to the therapeutic polypeptide typically has an affinity below 10 μM to human serum albumin and preferably below 1 μM. A range of albumin binding residues are known among linear and branched lipophilic moieties containing 4-40 carbon atoms, compound s with a cyclopentanophenanthrene skeleton, peptide having 10-30 amino acid residues etc (see paragraph [0035] of instant specification, as described above). Further, the specification discloses that albumin binding residue A is selected from pp. 13-17 (see specification filed 3/17/2006). The specification discloses that “the term hydrophilic spacer means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non-hydrogen atoms where 30-50% of these are either N or O (see paragraph [0036] of instant specification, as described above). The working examples describe GLP-1 (7-37) therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer  or $(CH_2)_4NH$-C(O)-$(CH_2)_3COOH$ (see paragraphs [0143]-[0195], [0197]-[0199], [0201]-[0203], [0205]-[0208]) and exendin-4 (1-39) therapeutic

polypeptide linked to an albumin binding residue via hydrophilic spacer

 or $CH_2)_4NH\text{-}C(O)\text{-}(CH_2)_3COOH$ (see paragraphs [0196], [0200], [0204]). Again, these examples all have either GLP-1 (7-37) and exendin-4, and linker

 or $CH_2)_4NH\text{-}C(O)\text{-}(CH_2)_3COOH$. The specification does not describe any other therapeutic polypeptide, or any other type of peptide or peptide-like molecule that act as GLP-1 agonist or react with human GLP-1 receptor; the specification does not describe any other linkers, any other reactive molecule or any other albumin binding residue. Descriptions of GLP-1(7-37) and GLP-1(7-37) analogs, Exendin-4(1-39) and ZP-10 and other therapeutic polypeptide listed on paragraph [0219] are not sufficient to encompass numerous other proteins that belong to the same genus. Again, claim 114 recites GLP-1 (7-35), GLP-1(7-36), GLP-1(7-37), GLP-1(7-38), GLP-1(7-40), GLP-1(7-41) and analogues thereof; claim 115 recites comprising no more than ten amino acid residues which have been exchanged, added or deleted, and claim 116 recites, no more than six amino acids. GLP-1 (7-37) have 31 amino acid residues. Thus, having no more than 10 amino acid residues exchanged, added or deleted, and no more than 6 amino acid residues changed, added or deleted, implies vast numbers of possibilities. For example, this implies that there are $10^{20} = 1 \text{ X } 10^{20}$ and $6^{20} = 3.65 \text{ X } 10^{15}$ different possibilities. Additionally, if 10 or 6 amino acids are added, then this implies that there are even more possibilities. Further, when non-natural amino acids such as D-isomers, β-amino acids, γ-amino acids and ε-amino acids are factored into the equation, there are innumerable possibilities. For linker (L),

anything that is lipophilic compound that binds the therapeutic polypeptide can be a linker. A linker can be any lengths, any composition and any formulation, anything that can form a bond. A linker can also be peptide sequences (forming peptide bonds). Thus, there are infinite numbers of linkers that are possible. For albumin binding residue, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus of therapeutic polypeptide and analogues thereof, lipophilic spacer, and an albumin binding residues claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

13. Claims 75-77, 83-89, 95, 100-105, 109, 111, 114-116, 118-119, 123, 126, 138, 140-141 are rejected are under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for GLP-1(7-37) and exendin-4 (1-39), does not

reasonably provide enablement for all therapeutic polypeptide. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (5) the breadth of the claims:

The claims are drawn to a compound which comprises a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer.

(2) The state of the prior art and (4) the predictability or unpredictability of the art:

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (Peptide Hormones, JA Parsons, Ed., 1976, 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study" (see p. 6). Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Additionally, Schinzel et al (FEBS, 1991, 286(1, 2): 125-128) teach that the substitution of Lys^{539} by an arginine caused a 600 fold reduction, substitution of Arg^{534} by a glutamine caused an even larger 7000-fold reduction of the catalytic rate while substrate binding remained essentially unaffected. The reference teaches that Arg^{534} to Gln exchange reduces the catalytic rate near to inactivity and even the conservative Lys^{534} to Arg exchange caused marked decrease of activity (see abstract).

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the

new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26)β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutatin in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6)β (see p. 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Additionally, the art recognizes that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study". Additionally,

SIGMA states that with regards to design of peptide sequences that, “Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine” (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Therefore, any modification on the polypeptide might have an affect on the polypeptide, thus vast numbers of experimentation would be required to see if the polypeptide modified with the oxime-containing non-natural amino acid would have the same affect on certain diseases as the wild-type polypeptide. As with all peptides, activity is based on the structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the peptide to be active. The sate of the art for prediction of the native conformation of the protein is, at best, a vague science. For example, in peptide chemistry, Ngo et al teach that for protein and peptides, a “'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task” (see p. 493). Accordingly, it is not known if an efficient algorithm for predicting the structure exists for a protein or peptide from its amino acid alone (see p. 492). Thus, activity of a given peptide cannot be based on its structure alone. Similarly, the Rudinger article (see the conclusion in particular) states “The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from the case to case by painstaking

experimental study." Finally, in an article published in Science, the author concluded that "one of the 'grand challenges' of high-performance computing-predicting the structure of proteins-acquires much of the flavor of the Holy Grail-quest of the legendary knights of King Arthur. It is extremely desirable to possess but extremely elusive to obtain" (see p. 643 in Berendsen). Berendsen et al states "at the present level of sophistication, [homology modeling] are effective for only 25% of the proteins for which the amino acid sequence is known" (see p. 642). It is known that proteins fold into their native conformation spontaneously and within seconds. The underlying principle of folding is known in the art yet the art lacks the ability to mimic native folding process (see p. 642 in Berendsen). "[E]xisting computers cannot sample enough configurations in a reasonable time to come up with the thermodynamically stable native structure;…we are not too sure that the available force field descriptions, which we need to compute the energy of a each configuration, are accurate enough to come up with reliable free energy of a conformation" (see p. 642 in Berendsen). Berendsen et al discloses the principle of the "Levinthal's paradox" which states that if one was to assume that "three possible states for every flexible dihedral angle in the backbone of a 100 protein residue, the number of possible backbone configuration is 3^{200}. Even an incredibly fast computational or physical sample in 10^{-15}s would mean that complete sample would take 10^{80}s, which excides that age of the universe by more than 60 orders of magnitude." Other tools such as lattice models provide insight into principle of folding, but to provide no solutions to the real folding problems (see p. 643 in Berendsen). The art has recognized that even single point mutations can cause diverse

effects on peptide activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle cell anemia can be traced to a single point mutation at position six in the beta globulin protein. The instant application claims are open to oxime modification at any position of any therapeutic polypeptides. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type therapeutic polypeptides.

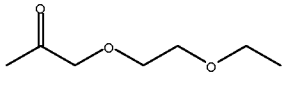
Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s), addition or deletion in a peptide or protein and linking the hydrophilic spacer within the peptide sequence, with regards to structure, function, or physical/chemical properties. Therefore, making any compound comprising therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer that has the same activity as the claimed peptide, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

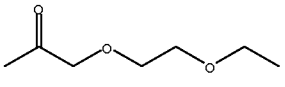
(3) The relative skill of those in the art:

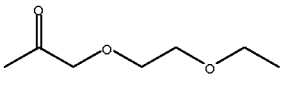
The relative skill of those in the art is high.

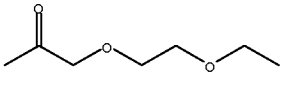
(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification discloses that “the term therapeutic polypeptide means a polypeptide which is being developed for therapeutic use, or which has been developed for therapeutic use" (see paragraph [0037] of instant specification US 2007/0203058 A1). Further, the specification discloses that "polypeptide and peptide means a compound composed of at least five constituent amino acids connected by peptide bonds" (see paragraph [0038] of instant specification as described above). The specification discloses that “the term analogue referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and/or wherein one or more amino acid residues have been deleted from thee peptide and or wherein one or more amino acid residues have been added to the peptide” (see paragraph [0039] of instant specification, as described above). The specification further discloses that “in one embodiment of the present invention the therapeutic polypeptide is a GLP-1 peptide” “GLP-1 peptide comprising the amino acid sequence of the formula (IV) (SEQ ID NO: 2), formula (V) (SEQ ID NO: 3), exendin-4 (SEQ ID NO: 4), ZP-10, SEQ ID NO: 5, GLP-2, human insulin or an analogue thereof, human insulin, human growth hormone or an analogue

thereof, parathyroid hormone or an analogue thereof, human follicle stimulating hormone or an analogue thereof, and a list of polypeptide such as trypsin, papain (see paragraphs [0119]-[0219]). Claim 115 recites, "a compound wherein said GLP-1 peptide comprises no more than ten amino acid residues which have been exchanged, added or deleted as compared to GLP-1 (7-37) (SEQ ID NO: 1); claim 116 recites "a compound wherein said GLP-1 peptide comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1 (7-37) (SEQ ID NO: 1). The specification is limited to  and $(CH_2)_4NH$-C(O)-$(CH_2)_3COOH$ as the linker. The specification discloses that an albumin binding residue is "a residue which binds non-covalently to human serum albumin. The albumin biding residue attached to the therapeutic polypeptide typically has an affinity below 10 μM to human serum albumin and preferably below 1 μM. A range of albumin binding residues are known among linear and branched lipophilic moieties containing 4-40 carbon atoms, compound s with a cyclopentanophenanthrene skeleton, peptide having 10-30 amino acid residues etc (see paragraph [0035] of instant specification, as described above). Further, the specification discloses that albumin binding residue A is selected from pp. 13-17 (see specification filed 3/17/2006). The specification discloses that "the term hydrophilic spacer means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non-hydrogen atoms where 30-50% of these are either N or O (see paragraph [0036] of instant specification, as described above). The working examples describe GLP-1 (7-37) therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer

 or $(CH_2)_4NH$-C(O)-$(CH_2)_3COOH$ (see paragraphs [0143]-[0195], [0197]-[0199], [0201]-[0203], [0205]-[0208]) and exendin-4 (1-39) therapeutic polypeptide linked to an albumin binding residue via hydrophilic spacer

 or $CH_2)_4NH$-C(O)-$(CH_2)_3COOH$ (see paragraphs [0196], [0200], [0204]). Again, these examples all have either GLP-1 (7-37) and exendin-4, and linker

 or $CH_2)_4NH$-C(O)-$(CH_2)_3COOH$. Working example 66 discloses GLP-1(7-37) derivative. Pharmacokinetic testing of GLP-1 analogue is dissolved in a vehicle suitable for subcutaneous or intravenous administration (see Example 66).

The specification does not describe any other therapeutic polypeptide, or any other type of peptide or peptide-like molecule; the specification does not describe any other linkers, any other reactive molecule or any other albumin binding residue. Descriptions of GLP-1(7-37) and GLP-1(7-37) analogs, Exendin-4(1-39) and ZP-10 and other therapeutic polypeptide listed on paragraph [0219] are not sufficient to encompass numerous other proteins that belong to the same genus. Again, claim 114 recites GLP-1 (7-35), GLP-1(7-36), GLP-1(7-37), GLP-1(7-38), GLP-1(7-40), GLP-1(7-41) and analogues thereof; claim 115 recites comprising no more than ten amino acid residues which have been exchanged, added or deleted, and claim 116 recites, no more than six amino acids. GLP-1 (7-37) have 31 amino acid residues. Thus, having no more than 10 amino acid residues exchanged, added or deleted, and no more than 6 amino acid residues changed, added or deleted, implies vast numbers of possibilities. For example,

this implies that there are 10^{20} = 1 X 10^{20} and 6^{20} = 3.65 X 10^{15} different possibilities. Additionally, if 10 or 6 amino acids are added, then this implies that there are even more possibilities. Further, when non-natural amino acids such as D-isomers, β-amino acids, γ-amino acids and ε-amino acids are factored into the equation, there are innumerable possibilities. For linker (L), anything that is lipophilic compound that binds the therapeutic polypeptide can be a linker. A linker can be any lengths, any composition and any formulation, anything that can form a bond. A linker can also be peptide sequences (forming peptide bonds). Thus, there are infinite numbers of linkers that are possible. For example, insulin has an A and a B chain conjugated by disulfide bonds. Therefore, insulin peptide has two C-terminal ends that may form bonds to chemical linker group and hydrophilic spacer. Furthermore, there are there are multiple lysines and arginines within the peptide sequence that may react with the hydrophilic spacer. Furthermore, the therapeutic polypeptides are different amino acids in lengths: FGF (GenBank Accession No. CAA41788) has 64 amino acid residues; erythropoietin (EPO) (GenBank CAA26095) has 193 amino acid residues; epidermal growth factor (GenBank CAA34902) has 71 amino acid residues. However, the claims and the instant specification do not recite where the attachments occur in these therapeutic polypeptides and still maintain activity. Vast numbers of therapeutic polypeptides comprise lysines and arginines that can react with linkers and where attachment points occur. Furthermore, for albumin binding residue, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. There is not sufficient amount of examples provided to enable one of ordinary skill in the

art to make and/or use a compound comprising a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer that would maintain its activity.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the reference above and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make a compound comprising a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer that would maintain the activity of the therapeutic polypeptide. Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any compound comprising any therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer that has the same activity as the claimed protein/polypeptide, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

14. Claims 76-77, 83-89 and 95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound of the formula or

pharmaceutically acceptable salt thereof, does not reasonably provide enablement for all prodrugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention and (2) the breadth of the claims:

The instant claims are drawn to a compound which comprises a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer – $(CH_2)_lD[(CH_2)_nE)_m(CH_2)_pQ_q$-, or a pharmaceutically acceptable salt or prodrug thereof.

The claims embrace a plurality of compounds and thus, a plurality of prodrugs of such compounds.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Han Hyo-Kyung (AAPS Pharmsci 2000, 2(1): 1-11 indicates that classical prodrug design often represents a nonspecific chemical approach to mask undesirable drug properties such as limited bioavailability, lack of site specificity, and chemical instability. Evolving strategies in targeted prodrug design includes antibody-directed enzyme prodrug therapy, gene-directed enzyme prodrug therapy, and peptide transport-associated prodrug therapy (see p. 1, Abstract). Han indicates that prodrugs can be designed to target specific enzymes or carriers by considering enzyme-substrate specificity to overcome various undesirable drug properties (see p. 2, left column). As indicated by Han reference, the prodrugs are structurally different. For example, glucose is a prodrug for hydrogen peroxide; hypoxanthine is a prodrug for superoxide, hydrogen peroxide; anygdalin is a prodrug for cyanide (see Table 1).

Since the prodrugs are structurally different making prodrugs of the any compound is an unpredictable process, where one cannot predict the prodrugs that may be possible, as the prodrug will have an effect on the activity and toxicity of the drug.

(5) The relative skill of those in the art:

Formation of salts is within the technical grasp of the artisan, however as there is no reliable means to predict what could be a prodrug of any compound, the level of skill in the art is low with regards to prodrugs.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for making the compounds, and the art recognizes the routine nature of forming pharmaceutical salts of compounds. However, the specification does not provide any examples of active and safe prodrugs, nor does the specification provide guidance as to how one would make prodrugs of the plurality of compounds. The compound which comprises a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer can have many different prodrugs. However, the specification does not provide any examples of prodrugs, nor does the specification provide guidance as to how one would make prodrugs of the plurality of compounds, particularly when as indicated by Han reference, the prodrugs are structurally different. Gucose is a prodrug for hydrogen peroxide; hypoxanthine is a prodrug for superoxide, hydrogen peroxide; anygdalin is a prodrug for cyanide (see Table 1).

More guidance is necessary as to make and use the prodrugs of compounds that comprise therapeutic polypeptides linked to an albumin biding residue via a hydrophilic spacer.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the reference above, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided

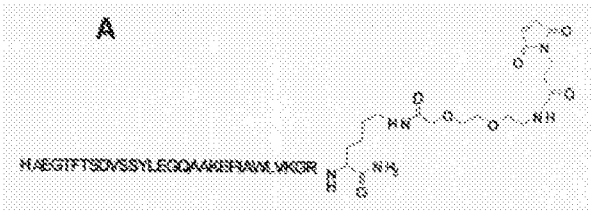
in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Rejection-35 U.S.C. 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 75-77, 83-89, 95, 100-105, 109, 111, 114-116, 126, 138, and 140-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al (Diabetes, Mar. 2003, 52(3): 751-759).

17. Kim et al teach a GLP-1 analog having the sequence HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRK conjugated to a human serum albumin (HAS) via a linker [2-[2-[2-maleimidopropionamido(ethoxy)ethoxy]acetamide through the epsilon amino group of Lys^{37}:  (see FIG. 1 and p. 753, both columns). This reads on claims 75-77, 83-89, 95, 109, 111, 114-116 and 126 since the reference teaches the GLP-1(7-37) compound structure attached to a human serum albumin via a hydrophilic spacer that is $CH_2O(CH_2)_2O(CH_2)_2$ where q is 0, and Y is C=O and W is -NHC(O)-. The reference teaches GLP-1, therefore, this meets

the limitation of claims 114-116 and 138. The reference teaches the subcutaneous injection and intraperitoneal, peritoneal and subcutaneous injections of the compound CJC-1131 (the compound above) to db/db mice (see Research Design and Method and p. 754, left column, top paragraph), meeting the limitation of claims 140-141. The instant specification discloses that "the term 'albumin binding residue' means a residue which binds non-covalently to human serum albumin. The albumin binding residue attached to the therapeutic polypeptide typically has an affinity below 10 μM to human serum albumin and preferably below 1 μM. A range of albumin binding residues are known among linear and branched lipophilic moieties containing 4-40 carbon atoms, compounds with a cyclopentanophenanthrene skeleton, peptides having 10-30 amino acid residues etc (see paragraph [0035] of instant specification US 2007/0203058 A1). Since the albumin binding residue is taught by the reference, linear alkyl moiety and is a lipophilic residue, this meets the limitation of claims 100-105.

18. Claims 75, 104, 105, 107, 109, 111, 114-116, 126, 138 and 140-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Glaesner et al (WO 02/46227 A2, file 11/29/01 and published 6/13/02).

19. Glaesner et al teach glucagon-like-1 compounds fused to proteins that have the effect of extending the in vivo half life of the peptides, and these fusion proteins can be used to treat non-insulin dependent diabetes mellitus (see abstract). The reference teaches GLP-1(7-37)-linker-HSA (see for example, Figure 3, lane 5). The human serum albumin (HSA) is selected from the group consisting of a) human albumin, b) human

albumin analogs, and c) fragment of human albumin and the C-terminus of the first polypeptide is fused to the N-terminus of the second polypeptide via a peptide linker (see p. 3, lines 29-35 and p. 4, lines 1-11). This meets the limitation of claims 75, 104-105, 107, 111, 114-116, since the peptide linker can form non-covalent bond with an amino acid residue of the HSA. Furthermore, the reference teaches the fragments of HSA: HSA (1-373), HSA (1-388), HSA (1-369), HSA (1-419), fragments between 1-369 and 1-419, HSA (1-177) and HSA (1-200) and fragments that include HSA (1-177) and HSA (1-200) (se p. 39). The reference further teaches that the fusion of GLP-1 compounds to large proteins such as the Fc region of an IgG or albumin not only acts to increase the half-life of the GLP-1 compound, but also contributes to the physical and conformational stability of the GLP-1 compound. For example, Val8-GLP-1-Linker-HSA in PBS is stable at 37°C out to about 30 days (see p. 61, lines 17-23). This reads on claims 140-141. Additionally, the reference teaches that the administration of compositions may be via any route known to be effective by the physician of ordinary skill. Peripheral, parenteral is one such method…peripheral parenteral routes can include intravenous, intramuscular, subcutaneous, and intraperitoneal routes of administration (see p. 62, lines 25-33). This meets the limitation of claims 140-141. Please note, the reference teaches that albumin binding residue is a peptide, the nonelected species of the instant claim 108. The reference teaches that modifications at amino acid side groups include, acylation of lysine, ε-amino groups, N-alkylation of arginine, histidine, or lysine (see p. 9, lines 22-28), meeting the limitation of claim 109.

Therefore, the reference anticipates claims 75, 104, 105, 107, 109, 111, 114-116, 126, 138 and 140-141.

20. Claims 75, 100-105, 107, 109, 111, 114-116, 118-119, 123, 126, 138, and 140-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Knudsen et al (Journal of Medicinal Chemistry, 2000, 43(9): 1664-1669, filed with IDS).

21. Knudsen et al teach a series of very potent derivatives of the 30-amino acid peptide hormone glucagon-like peptide-1 (GLP-1). The compounds have been derivatized with fatty acids in order to protract their action by facilitating binding to serum albumin; all compounds derivatized with fatty acids equal to or longer than 12 carbon atoms were very protracted compared to GLP-1 and thus seem suitable for once daily administration to type 2 diabetic patients (see abstract), meeting the limitation of claims 75, 100-105, 107, 111, 114-116. The reference teaches that Dipeptidyl peptidase IV (DPP-IV) rapidly degrades GLP-1(7-36)amide, rendering the rest of the molecule, GLP-1(9-36) amide, inactive (see p. 1664, right column). The reference teaches that "the principle of fatty acid derivatization has been used to protract the action of insulin by facilitating binding to serum albumin" (see p. 1665, left column), meeting the limitation of claims 118-119. The reference teaches that fatty acids or fatty diacids, optionally extended with a "spacer" between the e-amino group of the lysine side chain and the carboxyl group of the fatty acid. Furthermore, the reference teaches that "this extra negative charge added to the acylated molecule is also expected to provide a higher solubility at physiological pH" (see p. 1665, left column, "Discussion"), meeting

the limitation of claim 103. The reference teaches GLP-1 derivatized on position 8, 18, 23, 26, 27, 34,"36 or 38 with fatty acids and optionally a spacer (see Table 1), meeting the limitation of claims 109 and 123. The reference teaches that all compounds acylated with a fatty acid equal to or longer than 12 carbon atoms were considerable protracted compared to GLP-1, which had a half-life after sc administration of only 1.2h (see Table 2 and Figure 3). The reference teaches pharmacokinetic profile of selected compounds after sc administration to pigs (see Figure 3, and page 1666, left and right columns), therefore, meeting the limitation of claims 138, 140-141. Therefore, the reference anticipates claims 75, 100-105, 107, 109, 111, 114-116, 118-119, 123, 138, and 140-141.

22. Claims 75, 100-105, 107, 109, 111, 114-116, 123, 126, 138, and 140-141 are rejected under 35 U.S.C. 102(b) as being anticipated by Knudsen et al (WO 99/43341, filed with IDS).

23. WO 99/43341 teach GLP-1 attached to a lipophilic group through a spacer. WO '341 teaches that the lipophilic substituent attached to the GLP-1 moiety preferably comprises 4-40 carbon atoms; in particular 8-25 carbon atoms; attached to an amino group of the GLP-1 moiety by means of a carboxyl group …an amide bond with the e-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent (see page 16, bottom, and p. 17, lines 1-27). WO '341 teaches that this spacer is an unbranched alkane, α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, lipophilic substituent comprises a partially or completely

hydrogenated cyclopentanophenathrene skeleton, or a straight-chain or branched alkyl group (see claims 13-17, and page 17, lines 12-27). The WO '341 teaches that the lipophilic group may contain negatively charged groups (see page 17, lines 29-31). WO '341 teaches synthesis of such compounds as Arg^{34}, Lys^{26} (N^{ε}-(γ-glutamyl(N^{α}-lithochoyl)))GLP-1(7-37)-OH and Arg^{26},Lys^{34} (N^{ε}-glutamyl(N^{α}-hexadecanoyl)))GLP-1(7-37)-OH compounds (for example see Examples 5 and 6). The reference teaches a pharmaceutical composition for transdermal administration, meeting the limitations of claims 138 and 140-141. Therefore, WO '341 meets the limitation of claims 75, 100-105, 107, 109, 111, 114-116, 123, 126, 138 and 140-141.

Obviousness Double Patenting

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 75-77, 83-89, 95, 100-105, 107, 109, 111, 114-116, 118-119, 123, 126, 128, 138 and 140-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 14-15, 25, 38 and 40 of copending Application No. 12/186,880. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one of ordinary skill in the art practiced the claimed invention of instant application, one would necessarily achieve the claimed invention of copending application, and vice versa.

26. Instant claims are drawn to a compound which comprises a therapeutic polypeptide linked to an albumin binding residue via a hydrophilic spacer. The dependent claims are drawn to wherein the therapeutic polypeptides are GLP-1 and Exendin-4.

27. Copending claims are drawn to a compound of formula GLP-1 agonist-L-RR-protraction protein (I). The dependent claims recite the same GLP-1 agonist as the instant claims.

28. Therefore, if one of ordinary skill in the art practiced the instant claims, one would necessarily achieve the claimed invention of copending application, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

29. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Julie Ha/
Examiner, Art Unit 1654